Coincidentally, we recently reported a study that analyzed the relationships between coronary stenoses and vessel structure assessed by CTA, PET-derived MFR, and cardiovascular risk factors (2). We showed that abnormal wall structure affects regional MFR beyond the presence and severity of coronary stenoses. Specifically, coronary calcium content was the main determinant of regional MFR and a significant predictor of depressed global MFR. Interestingly, when the Framingham risk score, an indicator of overall cardiovascular risk, was considered; it remained the only significant determinant of global MFR, beyond CTA variables.

Although the 2 investigations are similar with regard to baseline characteristics of patients and differ only slightly in their methodology, they come to apparently different conclusions. In our view, however, both studies point to the effects of diffuse coronary atherosclerosis, in addition to those of focal significant stenoses, on myocardial perfusion.

Accordingly, depressed regional MFR is closely linked to the coronary atherosclerotic burden in the related vessel, described by the "summed stenosis score" in the study by Naya et al. (1) and by the coronary calcium content in ours (2). Moreover, global MFR is consistently related to different indicators of cardiovascular risk, the Duke CAD index in the study by Naya et al. (1), and the Framingham risk score in ours (2).

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Reply

We appreciate the commentary by Drs. Liga and Neglia regarding the relationship between coronary anatomic features and quantitative myocardial flow reserve (MFR) as assessed by cardiac hybrid positron emission tomography/computed tomography. We agree that both studies consistently demonstrate that the total burden of atherosclerosis, quantified with coronary calcium score (1) or by the total stenosis score, which integrates the effects of serial plaques (2), contributes to downstream MFR more than stenosis severity alone. However, we would not characterize MFR as being "closely linked to atherosclerotic burden." Rather, both studies as well as other studies using invasive angiography (3) have demonstrated that the correlation between epicardial stenosis severity and quantitative measures of perfusion, although significant, is only modest in magnitude. This is likely due to the fact that anatomic descriptors of epicardial stenosis cannot capture the effects of diffuse atherosclerosis on vasodilator function of either the epicardial coronary arteries or the microvasculature. Nonetheless, we believe that both studies add valuable insights to the literature regarding the determinants and role of MFR, which will have increasing clinical application given its powerful prognostic significance (4).

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Limitations of Noninvasive Measurement of Fractional Flow Reserve From Coronary Computed Tomography Angiography

We read with interest the paper by Koo et al. (1) regarding the diagnostic accuracy of noninvasive measurement of fractional flow reserve (FFR) from coronary computed tomography angiography data (FFR_{CT}). We do recognize the potential clinical and economic relevance of the validation of a diagnostic tool able to noninvasively determine the presence of ischemia-inducing coronary lesions because it would dramatically reduce the number of diagnostic angiograms and guide subsequent coronary revascularization. However, we have some concerns regarding the interpretation of the results of the study.

First, the major potential drawback of FFR_{CT} relates to the fact that FFR is calculated during "simulated" and not "real" hyperemia. To this end, the authors assume that "microcirculation reacts predictably to maximal hyperemic conditions in patients with normal coronary flow." This sentence is substantiated by a bibliographic reference that demonstrates the reproducibility of the

measurement of coronary flow reserve (CFR) using different agents but not its interpatient reproducibility (2). In contrast, it is well-known that CFR is extremely variable in different patients, being influenced, among the other things, by risk factors and age (3,4).

Second, the value of FFR is influenced not only by stenosis severity, but also by the amount of viable myocardium subtended by the epicardial coronary branch harboring the stenosis (5). This implies that a stenosis localized on the proximal left anterior descending coronary artery would have a completely different functional significance, and thus a different FFR, compared with an identical lesion on a second obtuse marginal branch. Similarly, the same stenosis would be associated with a different FFR value in the presence of viable or scarred myocardium (5). Of note, in the paper by Koo et al. (1), 17% of patients had a history of myocardial infarction.

Third, the incremental diagnostic yield of FFR is related to the evaluation of intermediate coronary stenoses (i.e., those usually ranging from 50% to 70% on visual angiographic assessment). In the paper by Koo et al. (1), less than one of third of all lesions were within this range on coronary computed tomography angiography evaluation. In the subset of coronary intermediate stenoses, although the overall accuracy of FFR_{CT} was still acceptable (83%), the sensitivity and positive predictive value were quite low (66.7% for both). This challenges the clinical value of FFR_{CT} in the assessment of those lesions for which clear proof of functional significance is indeed needed.

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Reply

We thank Dr. De Caterina and colleagues for their interest in our study, which demonstrates a high diagnostic performance of a noninvasive method for computing fractional flow reserve (FFR) from coronary computed tomography angiograms (FFR_{CT}) (1). FFR_{CT} is calculated by computational simulation of adenosine-mediated hyperemia rather than by actual administration of adenosine. This allows FFR_{CT} to determine coronary flow and pressure without additional medications or image acquisition. Calculation of FFR_{CT} is enabled by a predictable response of adenosine to reduce microcirculatory resistance downstream of epicardial coronary arteries. As discussed in our paper, the microcirculation reacts predictably to maximal hyperemia in patients with normal coronary flow, which reflects the fact that the maximal potential *change* in peripheral resistance from baseline to hyperemic conditions is preserved for microcirculatory vascular beds. In patients without coronary artery disease, the change in epicardial resistance is small between rest and hyperemia and allows the establishment of the limits of maximal change in microcirculatory resistance achievable in patients with microcirculatory dysfunction. Notably, this concept underscores the very definition of FFR, which also assumes that hyperemic microcirculatory resistance distal to a stenosis is identical to the resistance in the hypothetical case that the coronary arteries have no stenosis.

We agree with Dr. De Caterina and colleagues that coronary flow reserve (CFR) demonstrates variability for different patients. CFR is a different metric from FFR, given its dependence on *all* factors that affect blood supply to the microcirculation, including aortic pressure, epicardial resistance, and microcirculatory resistance. In this regard, CFR may be abnormal even as the response of the microcirculation to adenosine remains normal.

We agree that FFR is influenced by "the amount of viable myocardium subtended by the epicardial coronary branch harboring the stenosis." This input condition is meticulously factored into all FFR_{CT} models by setting the resistance of a coronary artery distal to a stenosis to be inversely (but not linearly) related to the size of the distal vessel. As blood vessels adapt proportionally to flow, a vessel feeding a dysfunctional territory will decrease in caliber and result in increased resistance in FFR_{CT} models. This adaptive process is time dependent, and, thus, patients with recent myocardial infarctions were excluded from our study.

We disagree with the claim of Dr. De Caterina and colleagues that the utility of FFR is limited to lesions of intermediate stenosis. Angiographic stenosis is a highly unreliable surrogate for ischemia, in which a significant proportion of anatomically high-grade lesions do not cause ischemia. Application of FFR_{CT} to these lesions may be invaluable for avoiding unnecessary invasive procedures provoked by physiologically irrelevant lesions. Conversely, even for anatomically mild lesions, a non-negligible rate of ischemia is consistently noted. Application of FFR_{CT} to these lesions may identify patients whose lesions fall below an anatomic threshold of "severe" but who experience ischemic symptoms. In this regard, FFR_{CT} should be considered an invaluable adjunct to coronary computed tomography angiography for lesions in *all* stenosis categories.

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